**Chapter 5 Dosage Form Design: Biopharmaceutical and Pharmacokinetic Considerations**

Biologic response of drug is the result of an interaction between the drug and cell receptors or enzyme systems. The magnitude of the response is related to the concentration of the drug achieved at the site of its action. This in turn depends on the dosage of drug administered.**,** the extent of its absorption and distribution to the site andthe rate and extent of its elimination from the body.

**Biopharmaceutics**

In general, for a drug to exert its biologic effect, it must be transported by the body fluids, traverse the required biologic membrane barriers, escape widespread distribution to unwanted area, Endure (or Bear) metabolic attack, Penetrate in adequate concentration to the sites of action, and Interact in a specific fashion, causing an alteration of cellular function.

**ADME**

The absorption, distribution, biotransformation (metabolism), and elimination of a drug from the body are dynamic processes that continue from time a drug is taken until drug has been removed from the body entirely. The rates at which these processes (i.e. ADME) occur affect the onset, intensity, and duration of the drug’s activity within the body.

**Pharmacokinetics** is the area of study that describes the time course of drug concentration in the blood and tissues. The various body locations to which a drug travels may be viewed as separate compartments, each containing some fraction of the administered dose of drug. The transfer of drug from the blood to other body locations is generally a rapid and reversible process. The drug in the blood therefore exists in equilibrium with the drug in the other compartments. In this equilibrium state, the concentration of the drug in the blood may be quite different (greater or lesser) than in the other compartments. Generally, the rate of transfer of a drug from one compartment to another is proportional to the concentration of the drug in the compartment from which it exits; the greater the concentration, the greater is the amount of drug transfer.

**Metabolism**

Metabolism is the major process by which foreign substances, including drugs, are eliminate from the body. During metabolism a drug substance may be biotransformed into pharmaceutically active, Inactive metabolites, or both. Often, both the drug substance and its metabolite or metabolites are active and exert pharmacologic effects. In some instances, pharmacologically inactive drug (termed a prodrug) may be administered for the known effects of its active metabolites. Dipivefrin, for example, is a prodrug of epinephrine formed by the estrification of epinephrine and pivalic acid. This enhances the lipophilic character of the drug, and a consequence its penetration into the anterior chamber of the eye is 17 times that of epinephrine. Within the eye, dipiverfrin HCl is converted by enzymatic hydrolysis to epinephrine. The metabolism of a drug to inactive products is usually an irreversible process that culminates (terminates) in the excretion of the drug from the body, usually via the urine. The term elimination refers to both metabolism and excretion. Except with intravenous administration absorption and elimination occur simultaneously but at a different rates.

**Principles of drug absorption**

There are barriers before an administered drug can arrive at its site of action.These barriers are chiefly a succession ( a sequence) of biologic membranes such as those of the GI epithelium, lungs, blood, and brain.

**Classification of the body membranes:**

Those composed of several layers of cells, like the skin, those composed of a single layer of cells, like the intestinal epithelium; and those less than one cell thick, like membrane of a single cell. Although the chemistry of body membranes differs one from another, the membranes may be viewed in general as a biomolecular lipoid layer attached on both sides to a protein layer. Drugs are thought to penetrate these biologic membrane in two general ways; by passive diffusion and through specialized transport mechanisms.

**Passive diffusion**

The term passive diffusion is used to describe the passage of a (drug) molecules through a membrane that does not actively participate in the process. Drugs absorbed according to this method are said to be passively absorbed. The absorption process is driven by the concentration gradient (i.e., the differences in concentration) across the membrane, with passage of drug molecules occurring primarily from the side of high concentration. Most drugs pass by diffusion. Passive diffusion is described by Fick’s first law, which states that the rate of diffusion or transport across a membrane (dc/dt) is proportional to the difference in drug concentration on both sides of the membrane:

dc/dt = P (C1-C2)

Where C1 and C2 are the drug concentrations on each side of the membrane and P is a permeability coefficient or constant. C1 represent the compartment with the greater concentration of drug, and thus the transport of drug proceeds from compartment 1 (e.g., absorption site) to compartment 2 (e.g., blood).

The concentration of drug at the site of absorption (C1) is usually much greater than on the other side of membrane **because** ofthe rapid dilution of the drug in the blood and its subsequent distribution to the tissues, so for practical purposes the C1-C2  may be taken simply as that of C1 and the equation written in the standard form for a first-order rate equation:

-dc/dt = PC1  

So doubling the dose doubles the transfer rate. The magnitude of the **permeability constant (P)** depends on the diffusion coefficient of the drug (D), the thickness (h) and area of the absorbing membrane (A), and the permeability of the membrane to the particular drug or partition coefficient (K).



Because of the lipoid nature of the cell membrane, it is highly permeable to lipid-soluble substances.The rate of diffusion of a drug across the membrane depends not only on its concentration but also on the relative extent of its affinity for lipid and rejection of water (a high lipid partition coefficient).The greater its affinity for lipid and the more hydrophobic it is, the faster will be its rate of penetration into the lipid-rich membrane. **Erythromycine base**, for example, possesses a higher partition coefficient than other erythromycin compounds, for example, ostolate and gluceptate. Consequently, the base is the preferred agent for topical treatment of acne where penetration into the skin is desired.

Because biologic cells are also permeated by water and lipid-insoluble substances, it is thought that the membrane also contains water-filled pores or channels that permit the passage of these types of substances. As water-passes in bulk across a porous membrane, any dissolved solute with small enough molecules to traverse the pores passes in by **filtration**. Aqueous pores vary in size from membrane to membrane and thus in their individual permeability characteristics for certain drugs and other substances.

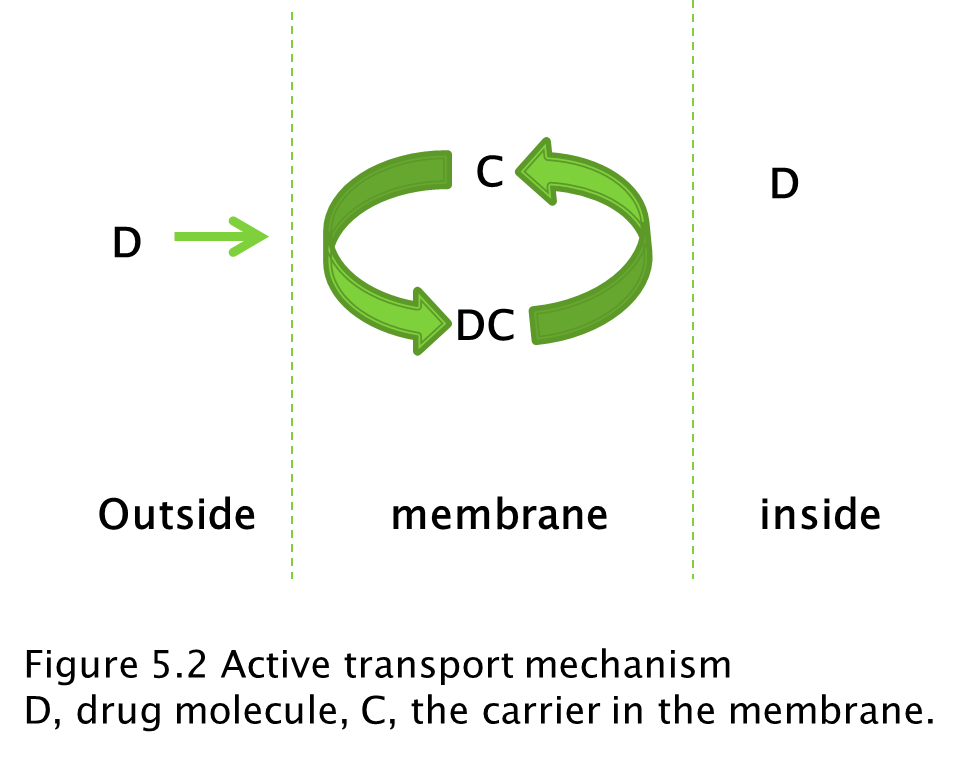
**pH and pKa of drug and permeation through biologic membrane**

Most drugs today are weak organic acids or bases, knowledge of their individual ionization or dissociation characteristics is important, because their absorption is governed to a large extent by their degree of ionization as they are presented to membrane barriers. Cell membrane are more permeable to the un-ionized forms of drugs and the highly charged nature of the cell membrane, which results in binding or repelling of the ionized drug and thereby decreases cell penetration. Also, ions become hydrated through association with water molecules, resulting in larger particles than the undissociated molecule and again decreased penetrating capability.

Degree of a drug’s ionization depends both on the pH of the solution in which it is presented to the biologic membrane and on the pka, or dissociation constant, of the drug (whether an acid or base). Since the pH of body fluids varies (stomach, pH 1; lumen of the intestine, pH 6.6; blood plasma, pH 7.4), the absorption of a drug from various body fluid will differ and may dictate to some extent the type of dosage form and the route of administration preferred for a given drug. It is often desirable for pharmaceutical scientists to make structural modifications in organic drugs and thereby favourably alter their lipid solubility, partition coefficients, and dissociation constants while maintaining the same basic pharmacologic activity. These efforts frequently result in increased absorption, better therapeutic response, and lower dosage.

**Specialized Transport Mechanisms**

This type of transfer seems to account for substances, many naturally occurring as amino acids and glucose, that are too lipid insoluble to dissolve in boundary and too large to flow or filter through the pores. This type of transport is thought to involve membrane components that may be enzymes or some other type of agent capable of forming a complex with the drug (or other agent) at the surface membrane.The complex moves across the membrane, where the drug is released, with the carrier returning to the original surface.



Specialized transport may be differentiated from passive transfer in that the former process may become saturated as the amount of carrier for a given substance becomes completely bound with that substance, resulting in a delay in transport. Other features of specialized transport include the specificity by a carrier for a particular type of chemical structure, so that if two substances are transported by the same mechanism or carrier, one will competitively inhibit the transport of the other.

**Active transport** as a subclassification of specialized transport denotes a process with the additional feature of the solute or drug being moved across the membrane against a concentration gradient, that is, from a solution of lower concentration to one of a higher concentration, or if the solute is an ion, against an electrochemical potential gradient. **Facilitated diffusion** is a specialized transport mechanism having all of the described characteristics except that the solute is not transferred against a concentration gradient and may attain the same concentration inside the cell as on the outside.

**Dissolution and drug absorption**

Dissolution is the process by which a drug particle dissolves. When the solubility of a drug depends on either an acidic or basic medium, the drug dissolves in the stomach or intestines respectively. Diffusion layer is a saturated layer creating from the dissolution of the drug molecules on the surface before entering into solution. From this diffusion layer the drug molecules pass throughout the dissolving fluid and make contact with the biologic membrane, and absorption goes on. If the dissolution of a given drug particle is rapid or if the drug is administered as a solution and remain present in the body as such, the rate at which the drug becomes absorbed depends on its ability to traverse the membrane barrier. If the rate of dissolution for a drug particle is slow because of the physicochemical characteristics of the drug substance or the dosage form, dissolution itself is a rate limiting step in absorption.

Drug remain in stomach from 2 to 4 hours. In small intestine the remaining time for drug from 4 to 10 hours. Slowly soluble drugs such as digoxin may not only be absorbed at a slow rate; they may be incompletely absorbed or in some cases largely unabsorbed following oral administration because of the natural limitation of time that they may remain within the stomach or the intestinal tract. Thus, poorly soluble drugs or poorly formulated drug products may be incompletely absorbed and pass unchanged out of the system via the feces. Changes in gastric emptying time and/or in intestinal motility can affect drug transit time and thus the opportunity for drug dissolution and absorption.These changes can affected by drugs. Certain drugs with anticholinergic properties for example dicyclomine HCl and amitriptyline HCl, can slow gastric emptying. This can enhance the rate of absorption from the stomach and reduce the rate of absorption from the small intestine. Alternatively, drugs that enhance gastric motility, for example laxatives, may cause some drugs to move through the gastrointestinal system and past their absorptive site at such a rate as to reduce the amount of drug absorbed. Gastric emptying time for a drug is rapid with fasting state. Decrease in gastric emptying time is advantageous for drugs absorbed from stomach but disadvantage for drugs prone to acid degradation, like penicillins and erythromycin, or inactivated by stomach enzymes, like l-dopa.

Dissolution rate increases by Increasing surface area (reducing the particle size), By increasing the solubility of drug in diffusion layer, by factors embodied in dissolution rate constant K, including the intensity of agitation of the solvent and diffusion coefficient of dissolving drug. For a given drug, the diffusion coefficient and usually concentration of the drug in diffusion layer will increase with increasing temperature. Increasing rate of agitation of the dissolving medium will increase the rate of dissolution. Reducing in the viscosity of solvent enhance dissolution rate of a drug. Changes in pH or nature of solvent that influence the solubility of the drug may be used to increase dissolution rate. Factors affecting dissolution of drug Surface Area, Crystal or Amorphous Drug Form, Salt Forms and Other Factors.

When a drug particle is broken up, the total surface area is increased For drug substances that are poorly or slowly soluble, this generally results in an increase in the rate of dissolution.To increase surface area, pharmaceutical manufacturers frequently use micronized powders in their solid product. Micronized powders consist of drug particles reduced in size to about 5 microns and smaller. The use of micronized drugs is not confined to oral preparations. For example, ophthalmic and topical ointments use micronized drugs for their preferred release characteristics and nonirritating quality after application.

Because of the different rates and degrees of absorption obtainable from drugs of various particle size, products of the same drug substance prepared by two or more reliable pharmaceutical manufacturers may result in different degree of therapeutic response in the same individual. A classic example of this occurs with phenytoin sodium capsules, which have two distinct forms.The first is the rapid-release type, that is, Prompt Phenytoin Sodium capsules, USP, and The second is the slow-dissolution type, that is, Extended Phenytoin Sodium Capsules, USP.

Solid drug materials may occur as:pure crystalline substances of definite identifiable shape or as amorphous particles without definite structure. Since the amorphous form of a chemical is usually more soluble than crystalline form, different extents of drug absorption may result with consequent differences in the degree of pharmacologic activity obtained from each.The hormone insulin presents another striking example of different degree of activity that may result from the use of different physical forms of the same medicinal agent. Insulin is protein that forms an extremely insoluble zinc-insulin complex when combined with zinc in the presence of acetate buffer. Depending on the pH of the acetate buffer, the complex may be an amorphous material. The amorphous form, or Prompt Insulin zinc suspension, USP, is rapidly absorbed upon intramuscular or subcutaneous (under the skin).The larger crystalline material, called ultralente insulin or Extended Insulin Zinc Suspension, USP, is more slowly absorbed and has a resultant longer duration of action. Intermediate-acting insulin can be obtained for example by a physical mixture of 70% of crystalline form and 30% of the amorphous form, called lente insulin or Insulin Zinc Suspension, USP, is intermediate acting and meets the requirements of many diabetics. Also available is a physical mixture of 50% of the crystalline form and 50% of the amorphous form.

Some crystalline are capable of forming different types of crystals, depending on the conditions (temperature, solvent, time) under which crystallization is induced. This property, whereby a single chemical substance may exist in more than one crystalline form, is **polymorphism**. The various polymorphic forms of the same chemical generally differ in many physical properties, including solubility and dissolution, which are of prime importance to the rate and extent of absorption. The use of metastable forms generally results in higher solubility and dissolution rates than the respective stable crystal forms of the same drug. On the other hand, the stable polymorph is more resistant to chemical degradation and because of its lower solubility is frequently preferred in pharmaceutical suspensions of insoluble drugs.

The dissolution rate of a salt form of a drug is generally quite different from that of the parent compound. Sodium and potassium salts of weak organic acids and hydrochloride salts of weak organic bases dissolve much more readily than do the respective free acid and base. The result is a more rapid saturation of the dissolving particle and the consequent more rapid diffusion of the drug to the absorption sites. Example: the addition of the ethylenediamine moiety to theophylline increases the water solubility fivefold. The use of the ethylenediamine salt of theophylline has allowed the development of oral aqueous solutions of theophylline and diminished the need to use hydroalcoholic mixtures such as elixirs.

Other Factors is The state of hydration of a drug molecule can affect its solubility and pattern of absorption. Usually the anhydrous form of an organic molecule is more readily soluble than the hydrated form. The rate of solubility and absorption for the anhydrous form of ampicillin for example was greater than that for the trihydrate form of the drug. The drug interaction with the normal components of the tract and any foodstuffs.For example chemical complex that may result in reduced drug solubility and decrease drug absorption. If the drug becomes adsorbed onto insoluble material in the tract, its availability for absorption may be correspondingly reduced. Example: complex formation between tetracycline and calcium, magnesium, and aluminum, resulting in decrease in absorption of the tetracycline.

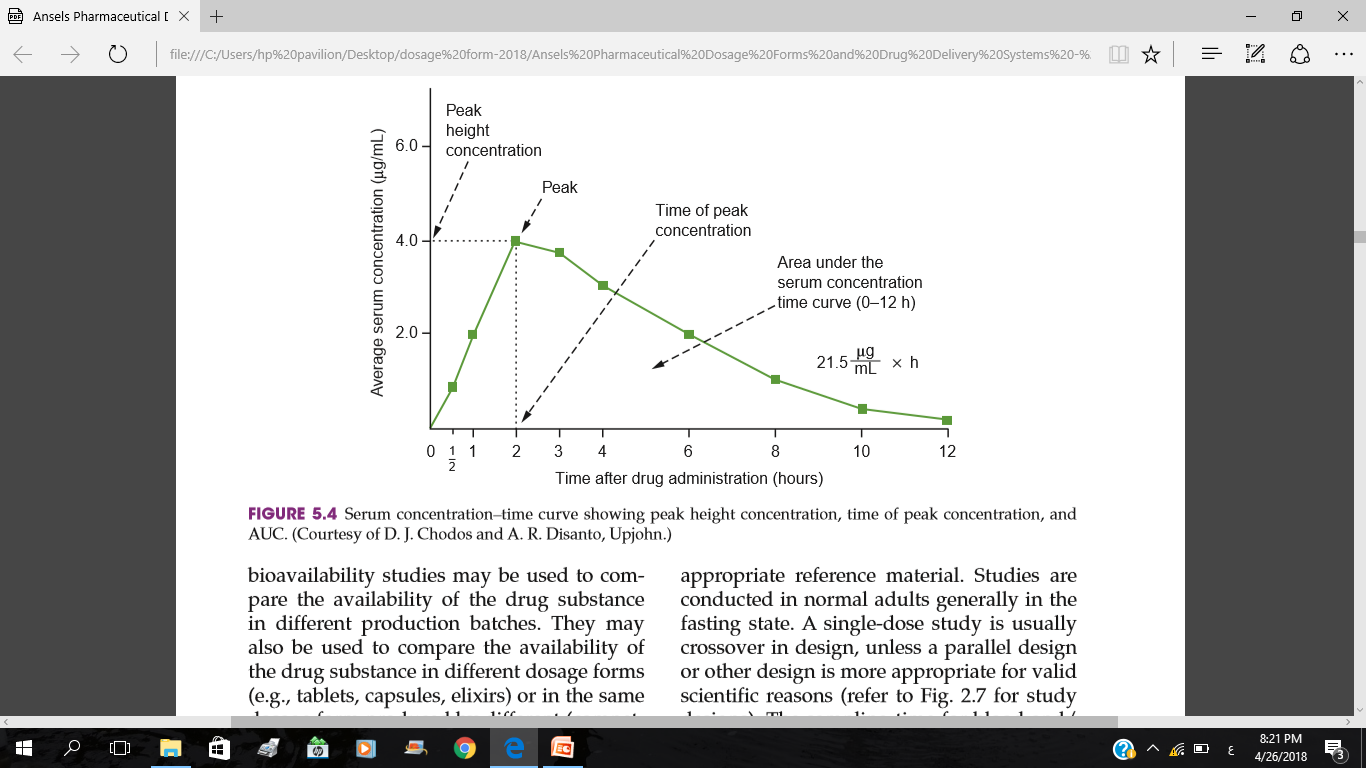
**Bioavailability and Bioequivalence**

Bioavailability - describe the rate and extent to which an active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of the drug action. Bioequivalence - refers to the comparison of bioavailabilities of different formulations, drug products, or batches of the same drug product. Bioavailability Data are used to determine The amount or proportion of drug absorbed from a formulation or dosage form, The rate at which the drug was absorbed, The duration of the drug’s presence in the biologic fluid or tissue; and, when correlated with patient response, The relationship between drug blood levels and clinical efficacy and toxicity,

According to the FDA (5), the in vivo bioavailability of a drug product may be determined by measurements of the concentration of the active drug ingredient, its therapeutic moiety, or its metabolite(s) in the blood or urine or by pharmacological effects. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements of the rate and extent to which the active drug moiety becomes available at the site of action. Two drug products may be considered bioequivalent if their rates and extents of absorption do not show a significant difference when administered at the same molar dose under similar experimental conditions, either single dose or multiple dose.

The FDA requires bioavailability data submissions in the following instances

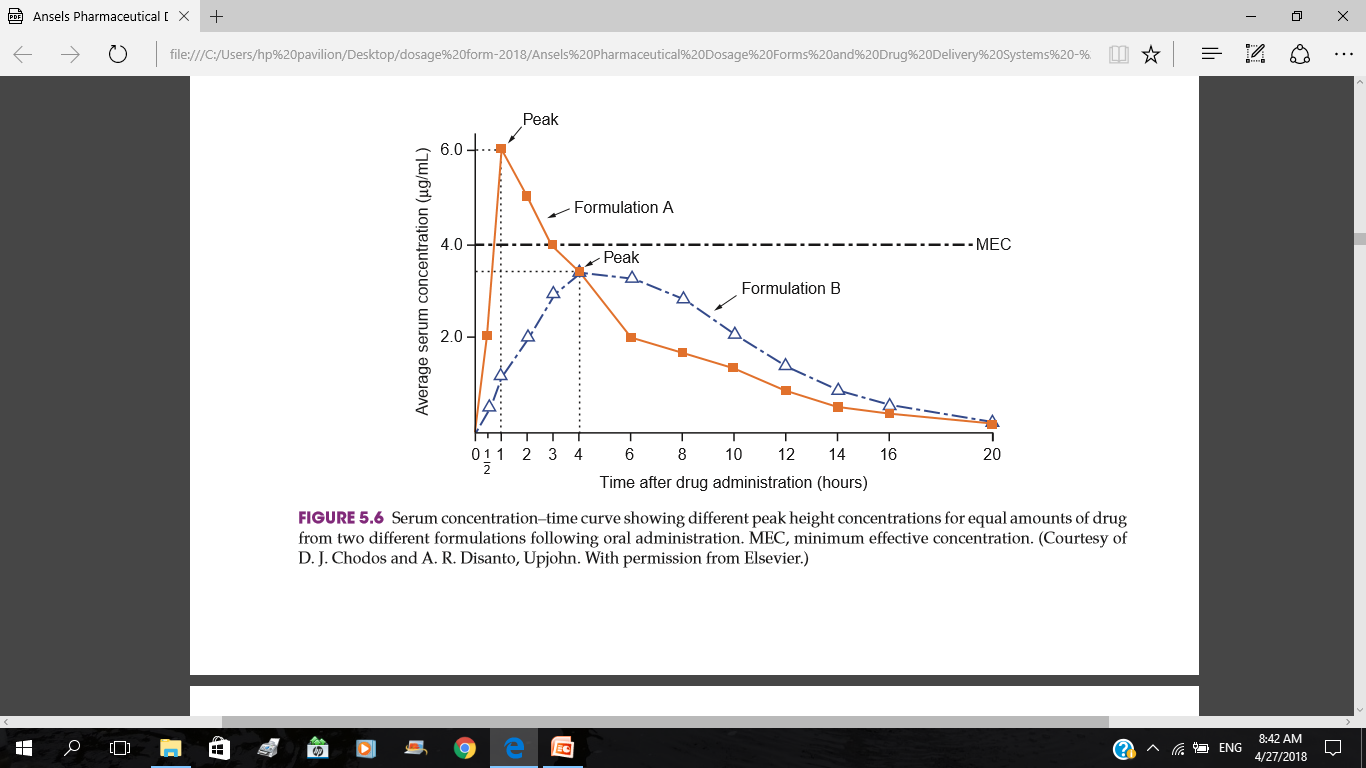
1. New drug application (NDAs)
2. Abbreviated new drug application (ANDAs)
3. Supplemental application: In vivo bioavailability data are required if there is a change in the following:
4. Manufacturing process, product formulation, or dosage strength beyond the variations provided for in the approved NDA.
5. Labeling to provide for a new indication for use of the drug product and if clinical studies are required, to support the new indication.
6. Labeling to provide for a new or additional dosage regimen for a special patient population (for example, infant) if clinical studies are required to support the new or additional dosage regimen.

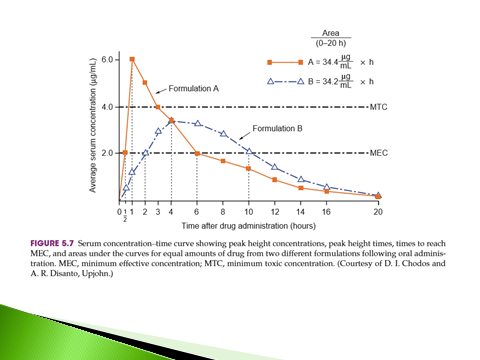


**Parameters for assessment and comparison of bioavailability**

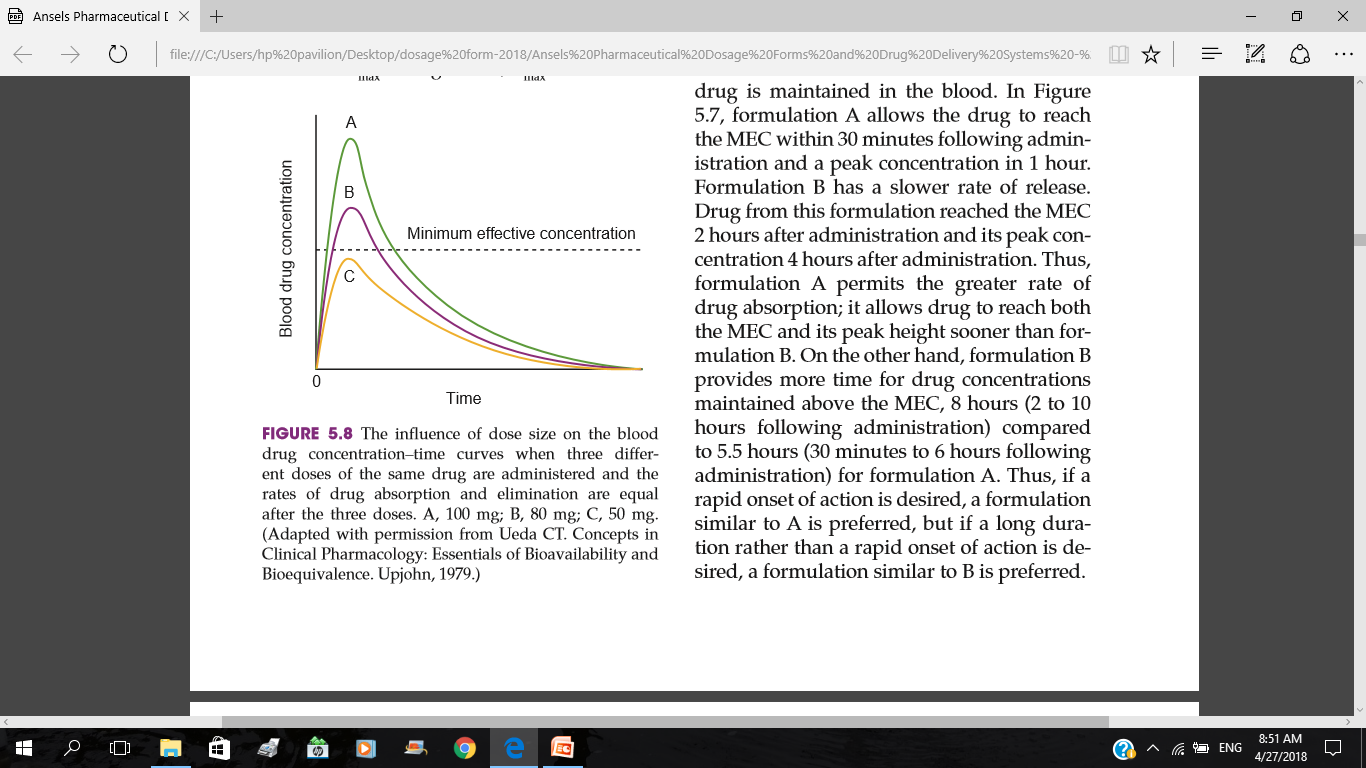
For comparative evaluation of the blood level curves following the oral administration of single doses of two formulations of the same drug entity the following parameters have been used The peak height concentration (Cmax), The time of the peak concentration (Tmax) and The area under the blood (or serum or plasma) concentration time curve (AUC). Using Figure 5.4 as an example, the height of the peak concentration is equivalent to 4.0 mg/mL of drug in the serum, the time of the peak concentration is 2 hours after administration, and the AUC from 0 to 12 hours is calculated as 21.5 mg/mL × hours.

Figure 5.6 depicts concentration–time curves showing different peak height concentrations for equal amounts of drug from two different formulations following oral administration. The horizontal line drawn across the figure indicates that the minimum effective concentration (MEC) for the drug substance is 4.0 mg/mL.Comparing the blood levels of drug achieved after oral administration of equal doses of formulations A and B in Figure 5.6, formulation A will achieve the required blood levels of drug to produce the desired pharmacologic effect, whereas formulation B will not. On the other hand, if the MEC for the drug is 2.0 mg/mL and the minimum toxic concentration (MTC) is 4.0 mg/mL, as depicted in Figure 5.7, equal doses of the two formulations result in toxic effects produced by formulation A but only desired effects by formulation B. The objective in the individual dosing of a patient is to achieve the MEC but not the MTC.



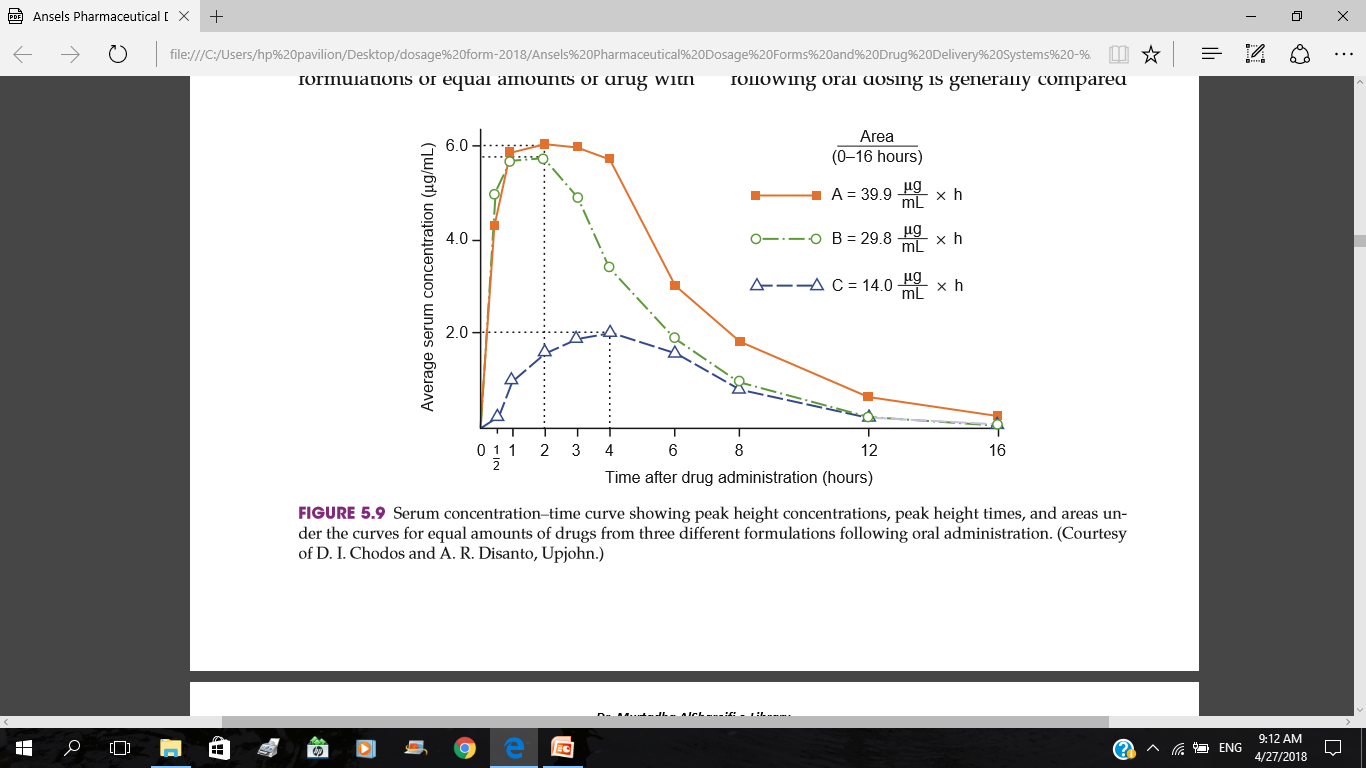


The size of the dose influences the blood level concentration and Cmax for that substance. Figure 5.8 depicts the influence of dose on the blood level–time curve for a hypothetical drug administered by the same route and in the same dosage form.As the dose increases, the Cmax is proportionately higher and the AUC proportionately greater. Tmax is the same for each dose.



The second important parameter in assessing the comparative bioavailability of two formulations is Tmax. In Figure 5.6, Tmax is 1 hour for formulation A and 4 hours for formulation B. This parameter reflects the rate of absorption from a formulation, which determines the time needed for the MEC to be reached and thus for initiation of the desired effect. The rate of absorption also influences the period over which the drug enters the bloodstream and therefore affects the duration that the drug is maintained in the blood.

The AUC of a concentration–time plot (Fig. 5.4) is considered representative of the total amount of drug absorbed into the circulation following the administration of a single dose of that drug. Equivalent doses of a drug, when fully absorbed, produce the same AUC. Thus, two curves dissimilar in terms of peak height and time of peak, like those in Figure 5.7, may be similar in terms of AUC and thus in the amount of drug absorbed. As indicated in Figure 5.7, the AUC for formulation A is 34.4 mg/mL × hours and for formulation B is 34.2 mg/mL × hours, essentially the same. If equivalent doses of drug in different formulations produce different AUC values, differences exist in the extent of absorption between the formulations. Figure 5.9 depicts concentration–time curves for three different formulations of equal amounts of drug with greatly different AUC. In this example, formulation A delivers a much greater amount of drug to the circulatory system than do the other two formulations. In general, the smaller the AUC, the lesser drug absorbed.



In practice, it is rare for a drug to be completely absorbed into the circulation following oral administration. As noted earlier, many drugs undergo a first-pass effect resulting in some degree of metabolic degradation before entering the general circulation. In addition, factors of product formulation, dissolution, chemical and physical interactions with the gastrointestinal contents, gastric emptying time, intestinal motility, and others limit the absorption of an administered dose of a drug.

**Bioequivalence of drug product**

The rate and extent to which a drug in a dosage form becomes available for biologic absorption or use depend in great measure on the materials in the formulation and on the method of manufacture.According to the USP, significant bioavailability and bioinequivalence problems that may be revealed through dissolution testing are generally the result of one or more of the following factors: the drug’s particle size, excessive amounts of a lubricant such as magnesium stearate in the formulation,coating materials, and inadequate amounts of tablet or capsule disintegrants.

**Pharmaceutical Equivalents** are drug products that contain identical amounts of the identical active drug ingredient, that is, the same salt or ester of the same therapeutic moiety, in identical dosage forms but not necessarily containing the same inactive ingredients, and that meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and where applicable content uniformity, disintegration times, and/or dissolution rates.

**Pharmaceutical Alternatives**  are drug products that contain the identical therapeutic moiety or its precursor but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own compendial or other applicable standard of identity, strength, quality, and purity, including potency and where applicable, content uniformity, disintegration times, and/or dissolution rates. **Bioequivalent Drug Products** are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the therapeutic moiety under similar experimental conditions, either single dose or multiple dose.**Therapeutic Equivalents** has been used to indicate pharmaceutical equivalents that provide essentially the same therapeutic effect when administered to the same individuals in the same dosage regimens.

**APPROVAL REQUIREMENTS FOR GENERIC DRUG PRODUCTS**

1. Contain the same active ingredients as the pioneer drug (inert ingredient may vary)

2. Be identical in strength, dosage form, and route of administration

3. Have the same indications and precautions for use and other labeling instructions

4. Be bioequivalent

5. Meet the same batch to batch requirements for identity, strength, purity, and quality

6. Be manufactured under the same strict standards of FDA’s CGMP regulations as required for pioneer products.

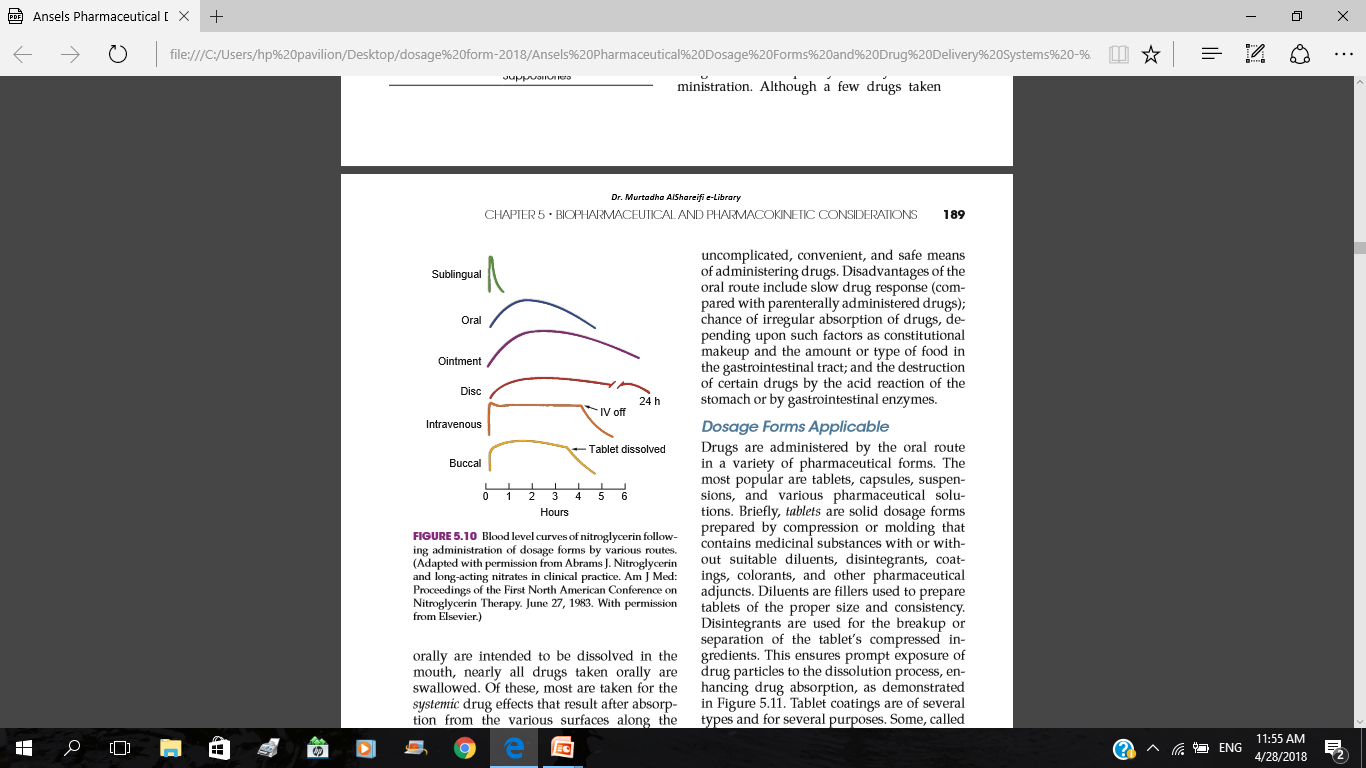
**Some Factors Which Can influence the Bioavailability Of Orally Administered Drugs**

1. **Drug substance physiochemical properties** which includes Particle size Crystalline or amorphous form , Salt form , Hydration, Lipid or water solubility and pH and pKa
2. **Pharmaceutic Ingredients** Fillers Binders Coatings Disintegrating agents Lubricants Suspending agents Surface active agents Flavoring agents Coloring agents Preservative agents Stabilizing agents
3. **Dosage form characteristics** Disintegration Rate (Tablets), Dissolution Time of Drug in Dosage Form, Product Age and storage Conditions
4. **Physiologic factors and patient characteristics** Gastric emptying time ,Intestinal Transit Time ,Gastrointestinal abnormality or pathologic condition ,Gastric contents, Other drugs, Food, Fluids Gastrointestinal pH
5. **Drug Metabolism (gut and during first passage through liver)**

**Route of drug administration**

Drugs may be administered using a variety of dosage forms and routes of administration.One of the fundamental considerations in dosage form design is whether the drug is intended for local or systemic effects.Local effects are achieved by direct application of the drug to the desired site of action, such as the eye, nose, or skin. Systemic effects result from the entrance of the drug into the circulatory system and transport to the cellular site of its action. For systemic effects, a drug may be placed directly in the bloodstream via intravenous injection or absorbed into the venous circulation following oral or other route of administration.

An individual drug substance may be formulated into multiple dosage forms that result in different drug absorption rates and times of onset, peak, and duration of action. Figure 5.10 and Table 5.6 demonstrate this for the drug nitroglycerin in various dosage forms. The sublingual, intravenous, and buccal forms present extremely rapid onsets of action, whereas the oral (swallowed), topical ointment, and topical patch present slower onsets of action but greater durations of action.The patch provides the longest duration of action, up to 14 hours following application of a single patch to the skin. The transdermal nitroglycerin patch allows a single daily dose, whereas the other forms require multiple dosing to maintain drug levels within the therapeutic window.



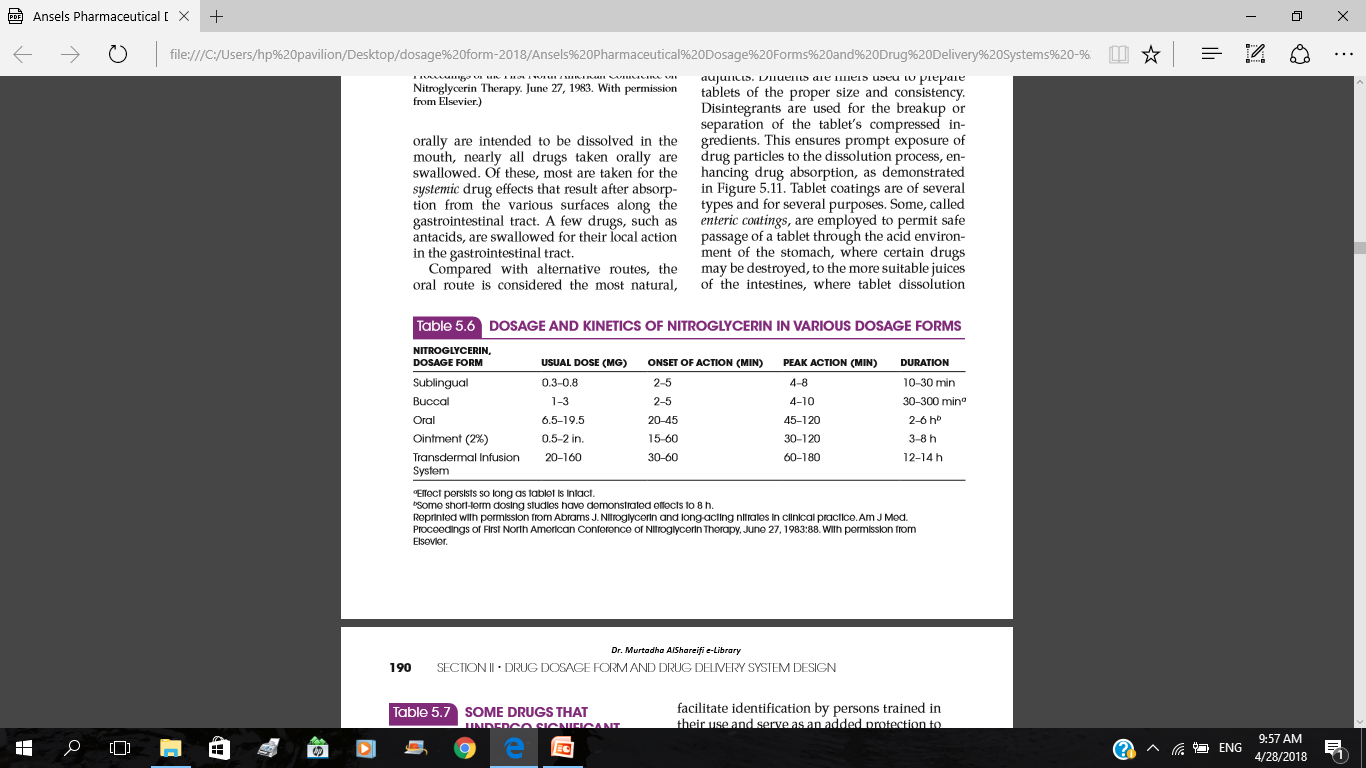
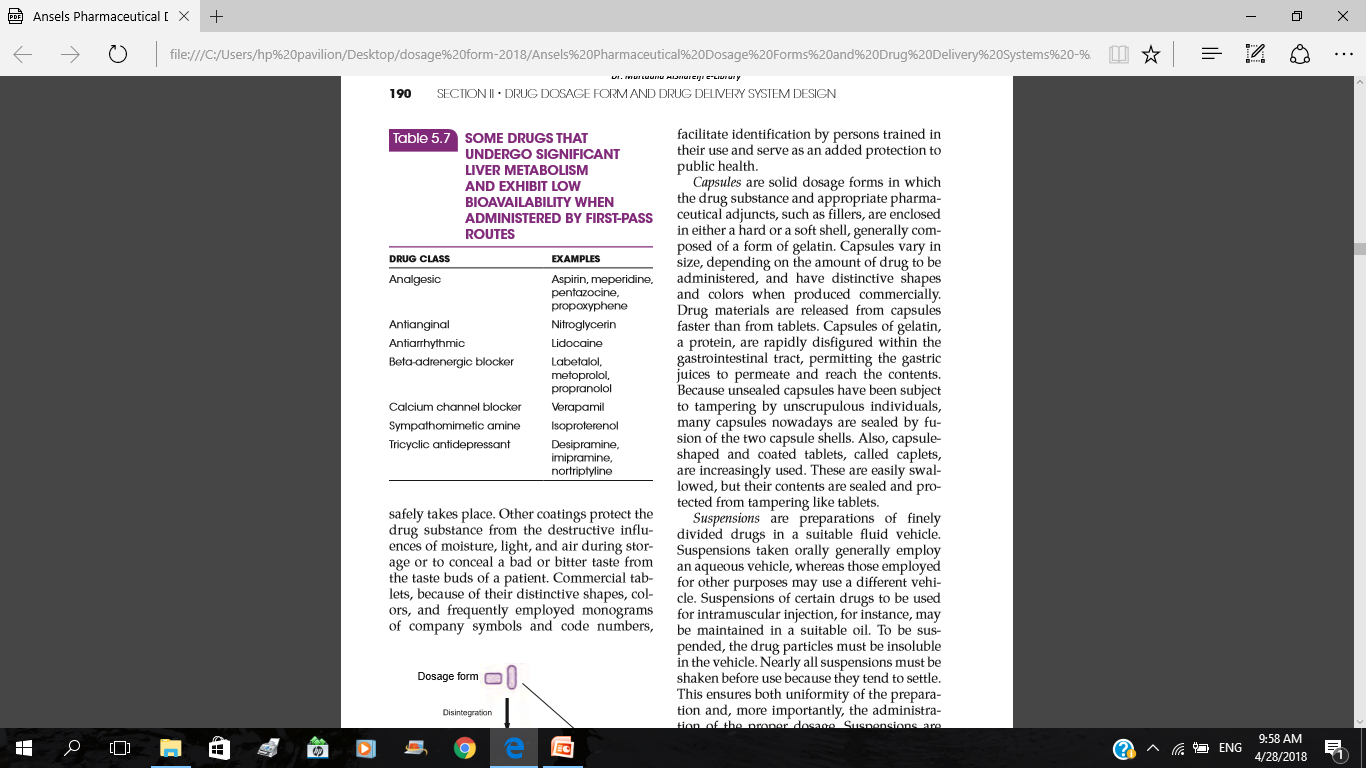


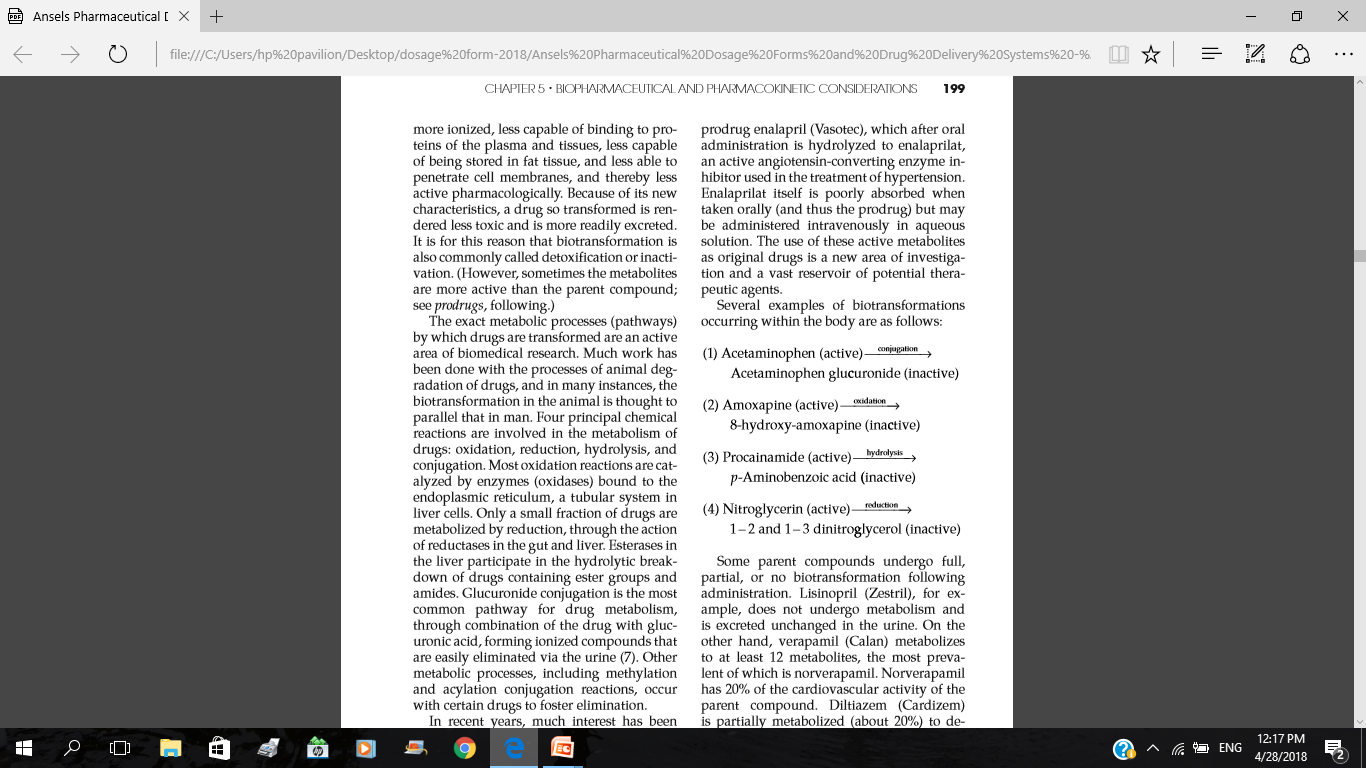
Table 5.7 lists some drugs according to their pharmacologic class that undergo a significant first-pass effect when administered by the oral routeTo compensate for this marked effect, the manufacturer may consider other routes of administration, for example, intravenous, intramuscular, or sublingual, that avoid the first-pass effect. Use of these routes must be accompanied by a corresponding adjustment in the dosage.



**Drug Metabolism or biotransformation**

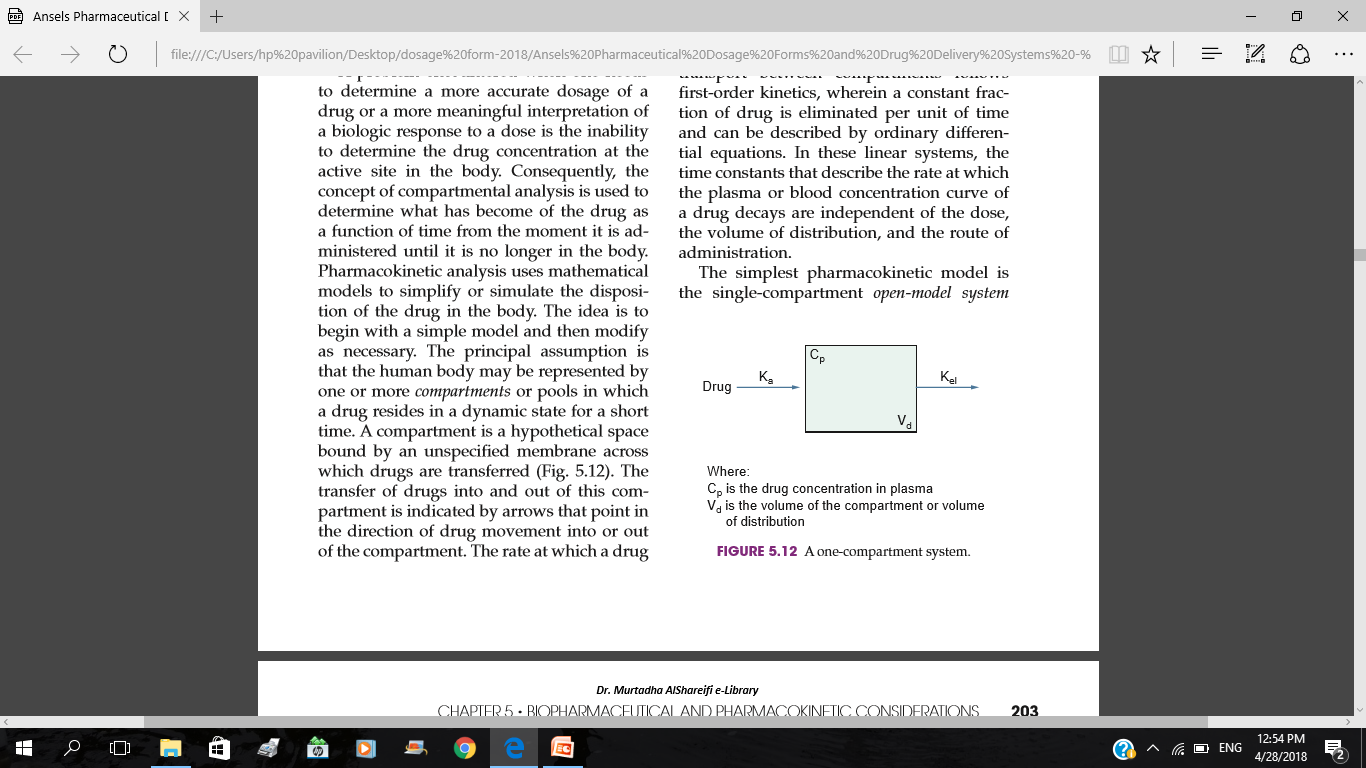
The biotransformation of a drug results in its conversion to one or more compounds that are more water soluble, more ionized, less capable of binding to proteins of the plasma and tissues, less capable of being stored in fat tissue, and less able to penetrate cell membranes, and thereby less active pharmacologically. Because of its new characteristics, a drug so transformed is rendered less toxic and is more readily excreted. It is for this reason that biotransformation is also commonly called detoxification or inactivation. (However, sometimes the metabolites are more active than the parent compound; see prodrugs, following.)

**Several examples of biotransformations occurring within the body are as follows**

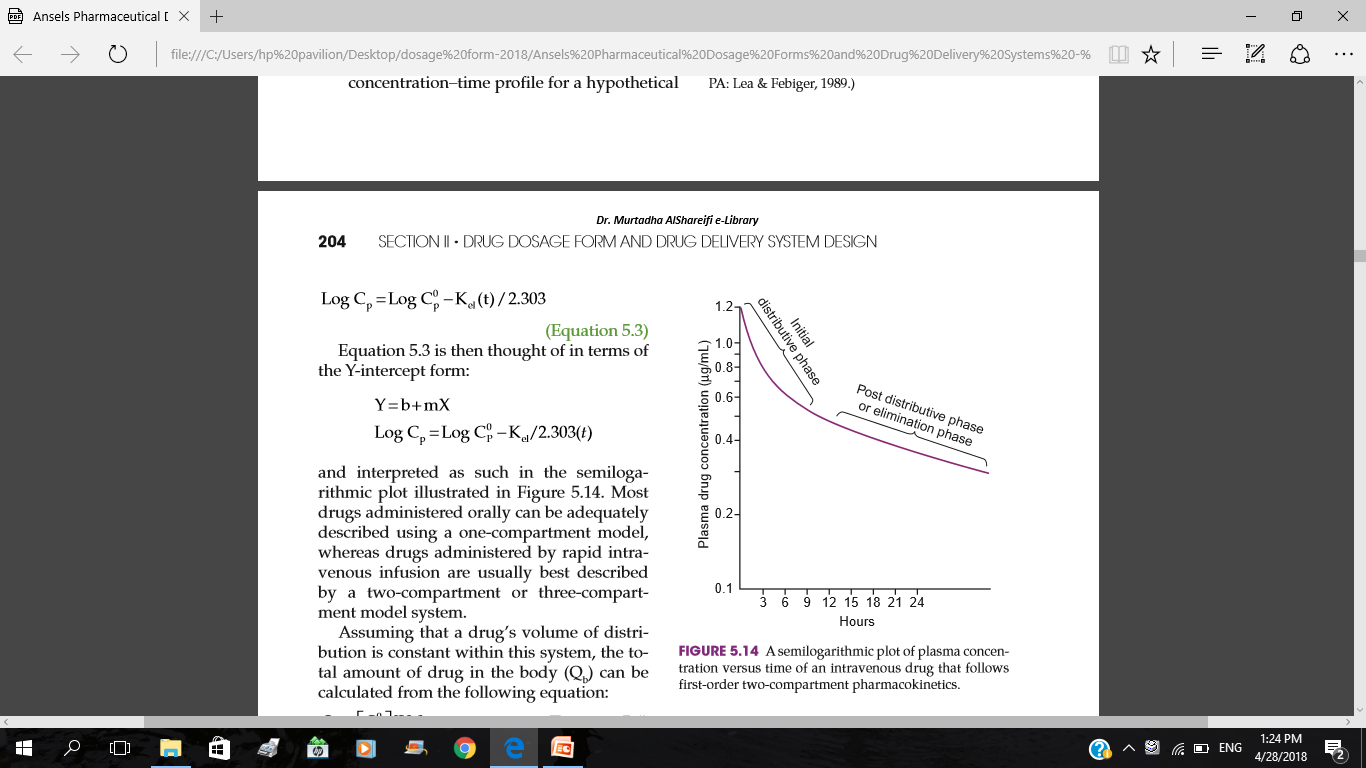


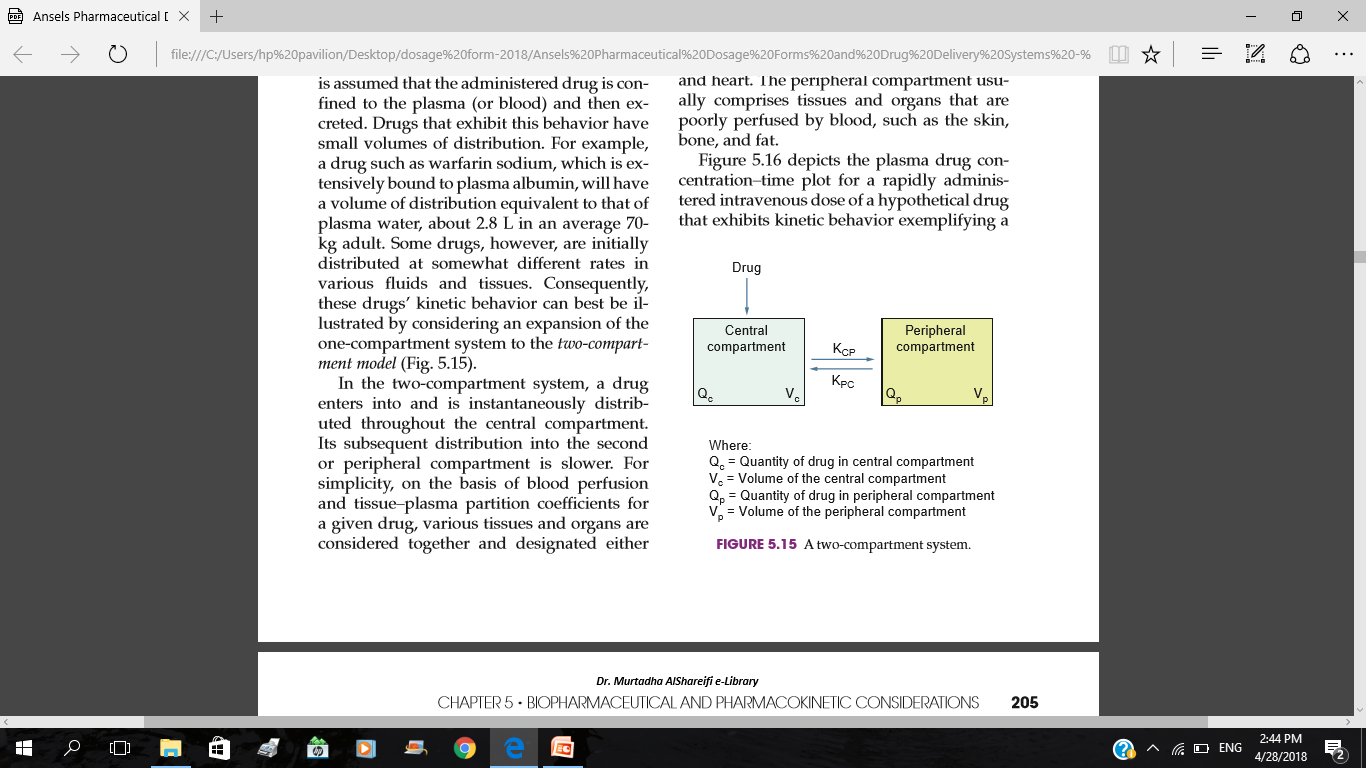
Pharmacokinetic principles

In compartment models, it is assumed that drug passes freely into and out of compartments. Thus, these compartmental systems are known as open systems. Typically, drug transport between compartments follows first-order kinetics, wherein a constant fraction of drug is eliminated per unit of time In these linear systems, the time constants that describe the rate at which the plasma or blood concentration curve of a drug decays are independent of the dose, the volume of distribution, and the route of administration. The simplest pharmacokinetic model is the single-compartment open-model system (Fig. 5.12). In this scheme, a drug can be instantaneously introduced into the compartment, that is, via rapid intravenous administration, or gradually, as with oral administration.In the former case, it is assumed that the drug distributes immediately to tissues and instantly attains equilibrium. In the latter case, the drug is absorbed at a certain rate and is characterized by the absorption rate constant Ka. Finally, the drug is eliminated from the compartment at a certain rate that is characterized by an elimination rate constant, Kel.



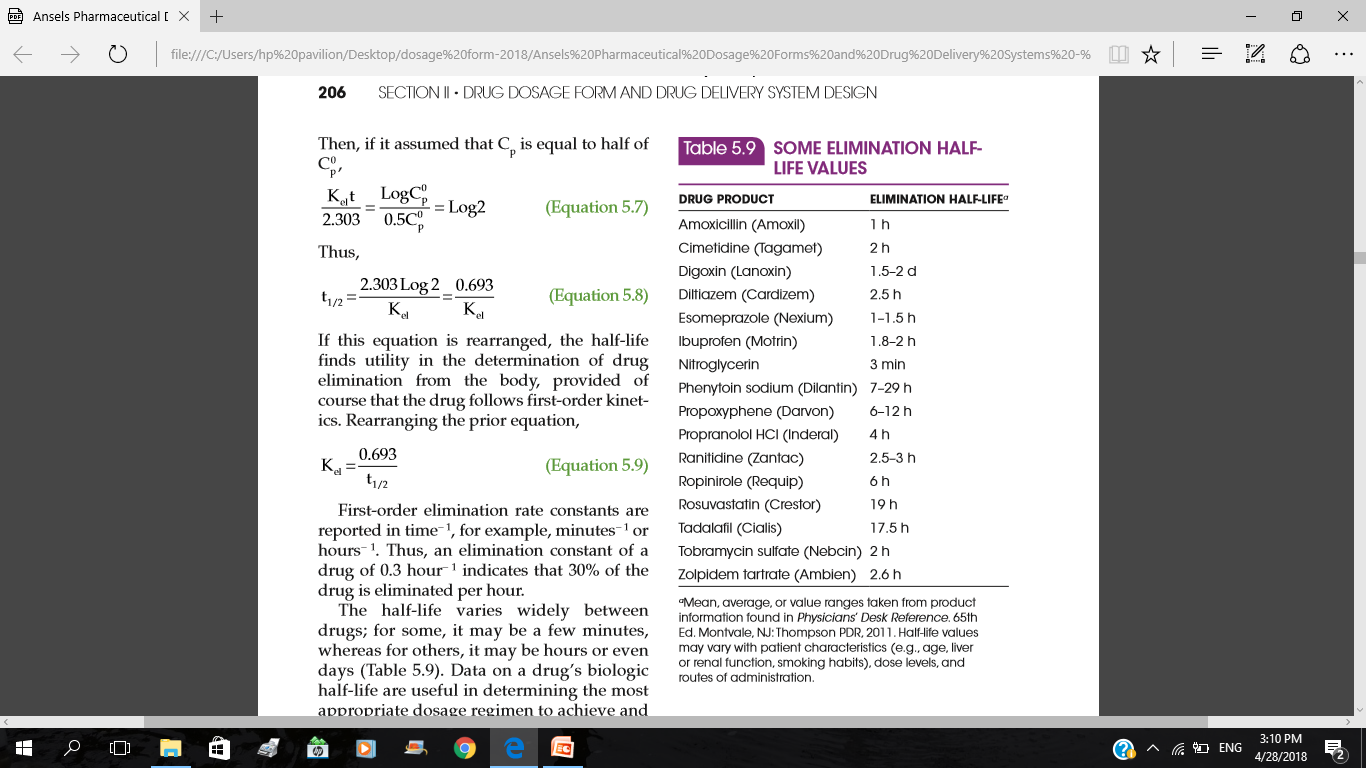
In this simple one-compartment system, it is assumed that the administered drug is confined to the plasma (or blood) and then excreted. Drugs that exhibit this behavior have small volumes of distribution. Some drugs, however, are initially distributed at somewhat different rates in various fluids and tissues. Consequently, these drugs’ kinetic behavior can best be illustrated by considering an expansion of the one-compartment system to the two-compartment model (Fig. 5.14 and 5.15).



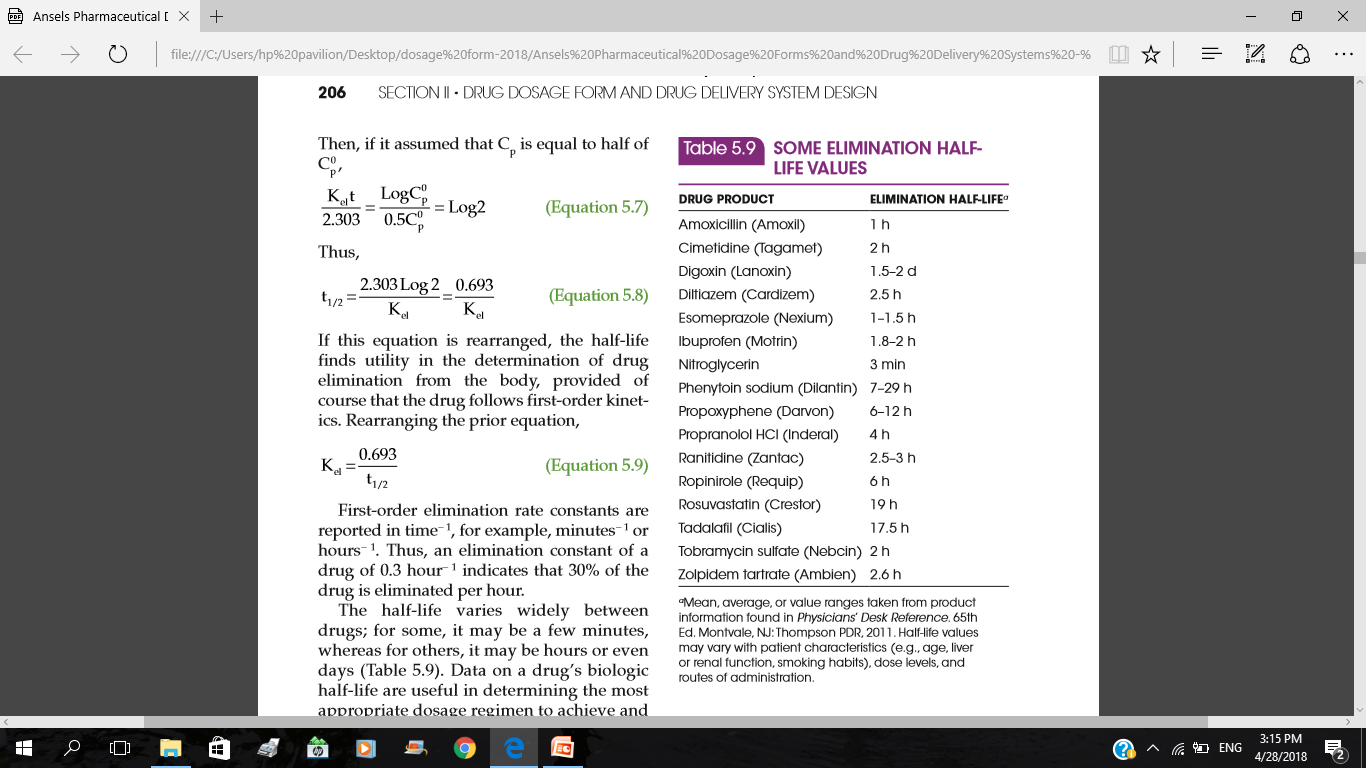


Half life

The half-life (t½) of a drug describes the time required for a drug’s blood or plasma concentration to decrease by half. This fall in drug concentration is a reflection of metabolic processes and/or excretion. The biologic half-life of a drug in the blood may be determined graphically from a pharmacokinetic plot of a drug’s blood concentration–time plot, typically after intravenous administration to a sample population. The amount of time required for the concentration of the drug to decrease by half is considered its half-life. The half-life can also be mathematically determined.

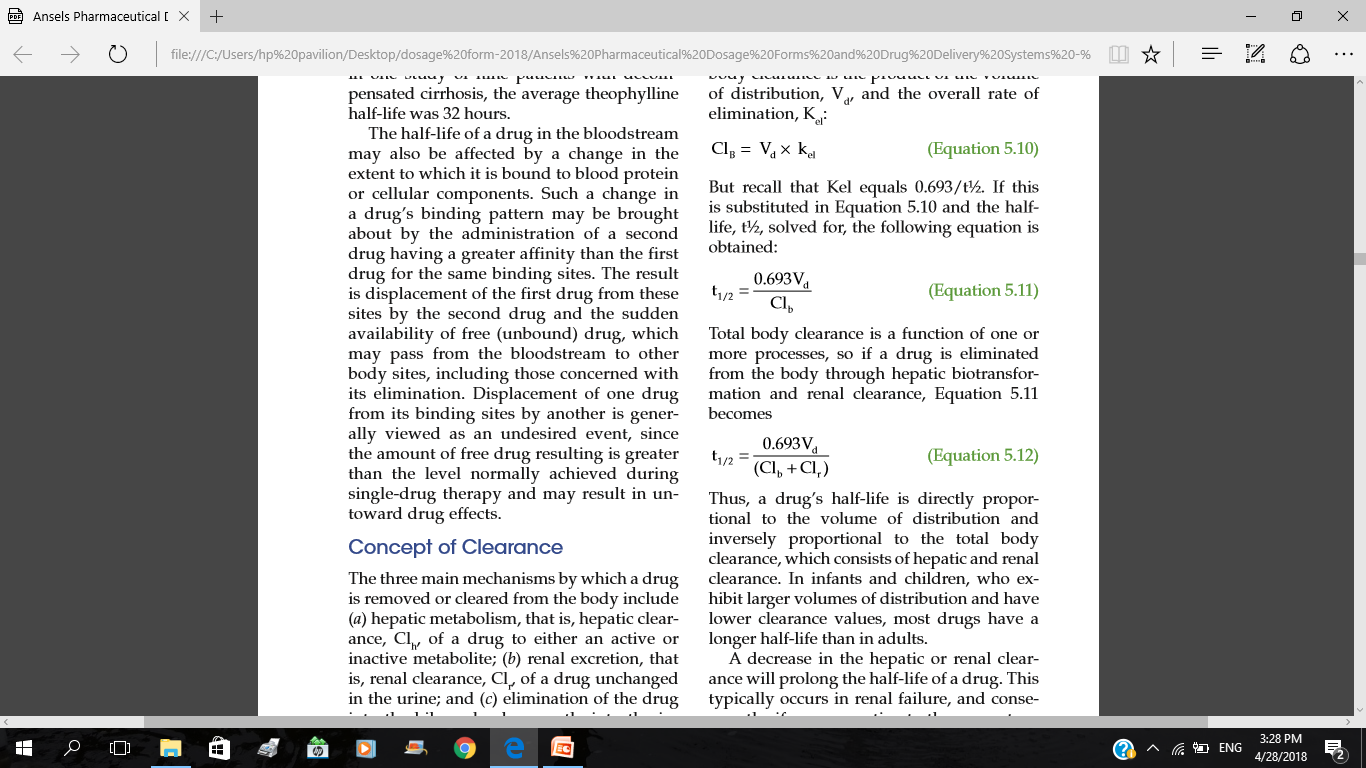


The half-life varies widely between drugs; for some, it may be a few minutes, whereas for others, it may be hours or even days (Table 5.9). Data on a drug’s biologic half-life are useful in determining the most appropriate dosage regimen to achieve and maintain the desired blood level. These determinations usually result in recommended dosage schedules for a drug, such as every 4, 6, or 8 hours.



Concept of clearance

The three main mechanisms by which a drug is removed or cleared from the body include (a) hepatic metabolism, that is, hepatic clearance, Clh, of a drug to either an active or inactive metabolite;(b) renal excretion, that is, renal clearance, Clr, of a drug unchanged in the urine; and(c) elimination of the drug into the bile and subsequently into the intestines for excretion in feces. These processes of elimination work together, so a drug that is eliminated by renal excretion and hepatic biotransformation will have an overall rate of elimination. Kel is the sum of the renal excretion, ku, and hepatic biotransformation, km. In the one compartment model described earlier, total body clearance is the product of the volume of distribution, Vd, and the overall rate of elimination, Kel:



Thus, a drug’s half-life is directly proportional to the volume of distribution and inversely proportional to the total body clearance, which consists of hepatic and renal clearance. In infants and children, who exhibit larger volumes of distribution and have lower clearance values, most drugs have a longer half-life than in adults. A decrease in the hepatic or renal clearance will prolong the half-life of a drug. This typically occurs in renal failure, and consequently, if one can estimate the percentage decrease in excretion due to renal failure, one can use Equation 5.11 to calculate the new half-life of the drug in the patient. Thus, an adjusted dosage regimen can be calculated to decrease the chance of drug toxicity.

**Dosage regimen consideration**

There are two basic approaches to the development of dosage regimens. The first is the empirical approach, which entails administration of a drug in a certain quantity, noting the therapeutic response and modifying the amount and interval of dosage accordingly.Besides the desired therapeutic effect, it is necessary to consider the occurrence and severity of side effects.

The second approach to the development of a dosage regimen is through the use of pharmacokinetics, or the kinetic approach. This approach is based on the assumption that the therapeutic and toxic effects of a drug are related to the amount of drug in the body or to the plasma (or serum) concentration of drug at the receptor site. Table 5.10 illustrates a number of factors that should be considered in the development of a dosage regimen. of these. Certainly, an important factor is the inherent activity, that is, pharmacodynamics and toxicity. A second consideration is the pharmacokinetics of the drug, which are influenced by the dosage form. The third factor focuses upon the patient to whom the drug will be given and encompasses the clinical state of the patient and how the patient will be managed. Finally, atypical factors may influence the dosage regimen. Collectively, all of these factors influence the dosage regimen.

